Current Practice

URINARY TRACT DISEASES

Maintenance Haemodialysis and Renal Transplantation

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During the last decade it has become apparent that a diagnosis of terminal renal failure is not necessarily a death sentence and that there are now techniques which can frequently prolong life indefinitely. Unfortunately these techniques are cumbersome and expensive in terms of staff and equipment and it is impossible to offer renal substitution to all the patients who could reasonably benefit. Perhaps half the 7,000 patients who die annually in the United Kingdom from chronic renal failure are unsuitable because of their extreme age or youth or because of the presence of other serious disease. The remainder are all more or less suitable for treatment, but at present only about one in five can be taken on. Selection policies vary widely but most units can usually accept only patients between the age of 15 and 50 years. Preference is given to the happily married patient with young children and particular emphasis is placed on the qualities of reliability, common sense, and stoicism. Many units, however, take patients as they present, accepting that psychiatric assessment of a uraemic patient may be impossible.

It is important to start dialysis at the correct time. If it is too early the patient will suffer the burdens and dangers without benefit, and if it is too late he may die or experience an unnecessary and dangerous illness. In practice it is reasonable to start when life on conservative management becomes dangerous or more unpleasant than it is on dialysis. This corresponds to a creatinine clearance below 3 ml./min. in a normotensive patient or below 6 ml./min. in one with hypertension. The inability to excrete more than 6 g. of urea in 24 hours must also be regarded as an indication.

The two techniques of maintenance haemodialysis and renal transplantation are complementary and most patients can be treated by either. Transplantation must be preceded by a period of dialysis and, if the graft fails, it should be possible to re-establish the patient on a machine.

Maintenance Haemodialysis

Principle

Substances of low molecular weight pass down a concentration gradient through a semipermeable membrane which retains larger particles. Heparinized blood flows over a cellulose-based membrane which separates it from dialysate containing sodium, calcium, magnesium, and chloride in roughly the same concentrations as in normal blood. Acetate is used as a buffer, and the fluid also contains potassium and glucose. Urea, creatinine, uric acid, phosphate, and other metabolites pass from the blood into the dialysate. Water is removed by ultrafiltration.

Types of Dialyser

The membranes may be arranged either in flat sheets (Fig. 1) or in tubes wound on a fibreglass support to form a coil

(Fig. 2). The flat-bed design is more difficult to assemble, but is cheaper to run and has a lower resistance to blood flow and a lower priming volume.

The dialysate may either be prepared as a single batch in a tank at the beginning of a dialysis or be made continuously by a proportionating pump. The pump is less cumbersome and easier to sterilize, but it is more expensive and requires continuous electrical monitoring. With both systems it is usual to monitor dialysate temperature, flow, and pressure and to include a photoelectric blood-leak detector in the effluent circuit. Finally the pressure at one or more points in the blood circuit is also monitored. All these devices are fitted with auditory alarms which can be set at appropriate limits; activation of these stops the dialysis until the alarm condition is corrected.

Dialysis Routine

Treatment must interfere as little as possible with the patient's normal life and is, ideally, undertaken at night while he is asleep. This is particularly important with a flat-bed dialyser, which should be used for three 10-hour spells each week. Coil dialysers are generally more powerful, and the shorter treatment times may be fitted in during the evenings.

The artificial kidney is much less flexible than its natural counterpart and is in use only intermittently. Consequently it is a poor substitute for normal renal function; the patient survives in a state of mild chronic renal failure and must take a diet moderately restricted in protein, sodium, and potassium and drink no more than one pint (570 ml.) daily.

Dialysis in the Hospital and at Home

Initially treatment is carried out in hospital, but, as the number of places is limited, it is desirable that patients be trained to run their machines at home. There should be available a room with a floor area of at least 90 sq. ft. (8.4 sq. metres) with water, drainage, and electricity, and, though many patients can manage entirely on their own, most dialysis units insist that a responsible assistant, usually the spouse, lives in the house during dialysis.

Medical Problems

Access to the Circulation.—This causes more problems than any other aspect of treatment. The arteriovenous Teflon-Silastic shunt (Fig. 3) is placed usually at the wrist or ankle. The two halves are connected together except when the patient is on dialysis, when the arterial and venous limbs are connected to the dialyser. Arterial pressure is sufficient to pump blood through a flat-bed dialyser but coil machines require a blood pump. Unfortunately the life of a shunt is limited, and most require surgical revision every few months—though some last two or three years. The usual problems are clotting and infection, and even if all is well the shunt is a permanent reminder of the patient's disability. Alternatively,

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a subcutaneous arteriovenous fistula may be created at the wrist and the dilated superficial veins cannulated at the beginning of each dialysis. Complications occur rarely and the patient may use his arm freely, but regular cannulation sometimes causes distress and may require more skill than some patients possess.

Anaemia.—Some degree of anaemia always exists and it is usual to find haemoglobin levels of 7-9 g./100 ml. All the factors mentioned in the section on chronic renal failure continue to operate and, in addition, a small amount of blood is left in the dialyser at the end of dialysis. This may lead to iron deficiency requiring treatment with parenteral iron. Blood transfusion is avoided except to cover major blood loss or surgery.

Hypertension.—Many patients start dialysis with severe hypertension which has failed to respond to treatment with

hypotensive drugs. Surprisingly this can usually be controlled completely by vigorous dietary sodium restriction (20-30 mEq daily) combined with adequate dialysis and it is unusual to need drug therapy. Occasional patients are controlled either with great difficulty or not at all and then require bilateral nephrectomy. Following this, control is always easier but salt excess can still lead to hypertension.

Reproductive Function.—Most women with severe chronic renal failure have amenorrhoea but, as their health improves, menstruation returns and may lead to significant blood loss during dialysis. Usually this can be prevented by the continuous administration of an oral contraceptive but a few patients require induction of a premature menopause or even hysterectomy. Fertility is reduced but not abolished, though no pregnancy has been carried to term. Men are both potent and fertile.

Infection.—Like any other patient with chronic renal failure the dialysis patient is unusually vulnerable to infection. In particular, his arteriovenous shunt provides a portal of entry with ready access to the circulation. Treatment must be prompt and take into account the altered pharmacology of the drug selected.

Following infection with the hepatitis virus the dialysis patient is prone to develop the carrier state. Only recently has it become possible to recognize these carriers, and cross infection between patients and staff has been a major problem. Obviously dialysis equipment should be shared as little as possible and the best solution is to move the patient out of the unit into the home.

The Disequilibrium Syndrome.—Rapid correction of biochemical abnormalities in the blood creates concentration gradients between the various compartments of the body. The usual manifestations are headache, vomiting, twitching, and occasionally fits, and this syndrome is a major factor limiting the power of dialysers and the time interval between dialyses.

Psychiatric.—Problems are frequent and arise partly because the patient resents his physical dependence on a machine and the dialysis unit, and partly because he is frustrated by the discipline that this treatment entails. Fear of the present and uncertainty about the future both play their parts. Familiarity with the technique helps to allay the fear and self dialysis at home establishes some degree of independence. An additional strain, however, falls on the spouse, who may feel responsible for the patient. Eventually, however, many families adapt to the dialysis to an astonishing extent and accept it simply as a tedious chore.

FIG. 1 (a).—A two-layer Kiil artificial kidney. This is a "flat plate" type of kidney, which is assembled sterile before use from the boards and membranes. These are clamped together in a stack. (b) The surface area is 1.2 sq. metres but it needs only 75 ml. of saline for priming the boards. Blood flows along the membrane through the kidney while the dialysate flows in the opposite direction in grooves in the kidney boards (c).

FIG. 2.—The Kolff-Travenol "twin coil" kidney. This has a membrane surface area of 1.9 sq. metres and needs 1,000-1,500 ml. of blood for priming. The coil has been opened out to show the layers of its structure—cellophane tubing and nylon net backing.

FIG. 3.—AN ARTERIOVENOUS SHUNT.

Bone Disease.—Renal osteodystrophy may lead to clinical problems, particularly if dialysis is inadequate. Some units, however, have more trouble than others and its pathogenesis is not fully understood. Secondary hyperparathyroidism is usually the most prominent component and may require parathyroidectomy.

Peripheral Neuropathy.—Again this is usually only a major problem in the underdialysed patient. Occasionally, however, a crippling neuropathy may develop despite excellent dialysis.

Cost

The cost is extremely high. If a flat-bed kidney is used the capital outlay, including monitoring and safety equipment, is £2,000 to £3,000 with an additional installation cost of about £500. The annual cost of disposable items is about £850. A coil dialyser is cheaper to buy and instal but more expensive to run. To these sums must be added depreciation and the cost of building, equipping, and staffing the hospital dialysis unit.

Prognosis

Patients have now been maintained on dialysis for more than ten years, and there is no obvious reason why this period should not be extended. There is an appreciable mortality (10%) during the first two months of treatment, but thereafter the death rate drops sharply and after one year becomes vanishingly small. As more elderly patients are accepted the mortality due to incidental, particularly vascular, disease may be expected to rise.

Renal Transplantation

The first successful transplants were carried out between identical twins more than 15 years ago. Since then there have been numerous attempts to graft kidneys from other relatives and from unrelated donors, but only in the past five years has there been any consistent degree of success. This difference is largely due to the phenomenon of rejection, and most recent work has been towards matching donor and recipient and developing drugs which suppress the reaction to the inevitable differences that remain.

The Recipient

Preparation of the recipient must include a period of adequate dialysis during which his condition can be improved and his lower urinary tract assessed. Bilateral nephrectomy may be performed if there is chronic urinary infection, vesico-ureteric reflux, calculi, polycystic kidneys, or severe hypertension.

The Donor

The best results are obtained when the kidney is obtained from a suitable first-degree relative. Many surgeons, however, are unhappy to remove a normal organ from a healthy person under any circumstances. In addition there may be doubt about the factors which have influenced the relative to offer a kidney, and most surgeons in the United Kingdom take most of their kidneys from cadaver "donors." The latter should be less than 70 years old, have good kidneys, and be free of transmissible disease. Nephrectomy must be performed within one hour of death and, after the kidneys have been irrigated with one of several different solutions, they may be stored on ice for up to ten hours. During this time, or even before the "donor" has actually died, tissue typing may be carried out and suitable recipients alerted.

Matching

Compatibility between recipient and donor in respect of the major blood groups is essential. In addition, histocompatibility antigens located on lymphocytes must be recognized and incompatibilities kept to a minimum. Unfortunately there are many of these antigens, known and unknown, in existence and it is probably impossible to obtain a perfect match. Successful transplantation, however, can occur despite the presence of definite incompatibilities.

The Operation

The ureter has a precarious blood supply and the donor kidney is placed extraperitoneally in the iliac fossa of the recipient. The vascular anastomoses are made to the internal iliac artery and the common or external iliac vein, and the ureter is implanted into the bladder via a suitable tunnel. In good hands technical failures are rare and the operation causes little disturbance to the patient. Postoperatively there is usually a period of impaired renal function, and most cadaver kidneys show a tubular necrosis which takes two or three weeks to resolve. During this time the dialysis routine is continued.

Immunosuppression

This is always necessary and is continued indefinitely. The mainstays are azathioprine and steroids; dosage schedules vary but generally the initial dose of azathioprine is the highest that the patient can tolerate, bearing in mind his renal function and blood count. Initial steroid doses may also be enormous (200 mg./day of prednisolone) but, if all goes well, dosage of both drugs is reduced. During rejection episodes immunosuppressive treatment is intensified and steroid doses in particular are increased. Local radiotherapy to the graft and systemic therapy with actinomycin C may also be used. Experience in France and the U.S.A. suggests that the addition of antilymphocyte serum will improve results substantially.

Complications

The usual complications of major surgery may appear but are rare, and the majority are attributable to the immunosuppressive treatment. Opportunistic infection with bacteria, fungi, viruses, and even protozoans may occur and occasionally lead to the death of the patient. Additional morbidity attributable to steroids may include peptic ulceration, osteoporosis, and aseptic necrosis of bone. In recent years the importance of tissue matching and the limitations of immunosuppressive treatment have both been realized and disasters occur rather less frequently. If a transplant fails the patient can be returned to dialysis and perhaps have another transplant later.

Prognosis

Techniques are changing rapidly and inevitably transplant survival figures which refer to operations carried out even two years ago are out of date by that number of years. Using live donors the best American series show good transplant function in 80 to 90% of cases at two years, while the same figure for kidneys from cadavers is about 60%. Most kidneys are lost in the first three months, and there is no obvious reason why these long survivors should not continue to function for many years.

Dialysis versus Transplantation

The patient with a good transplant leads a normal unrestricted life, which is in strong contrast to the life of even

the best dialysis patient. The happy state of the transplant recipient, however, is attained only at the cost of a real risk to his life. Most informed patients prefer to take this risk but at present it is not possible to offer transplantation to all. The major limiting factor is the availability of kidneys and if a patient presents at a time when there is a long queue of patients with his blood group he may be offered only home

dialysis. Expected difficulty with tissue matching or disease of the lower urinary tract are further reasons for diverting him in this direction.

FURTHER READING

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ANY QUESTIONS?

We publish below a selection of questions and answers of general interest.

Soft Water and Congenital Malformations

Q.—How strong is the evidence for an association between soft water and congenital abnormality?¹ Should women of childbearing age be advised not to drink water that has been treated by a water-softener?

A.—What evidence there is for an association between soft water and congenital malformation is based on the higher incidence of neural tube abnormalities in the north and west of England as compared with the home counties and East Anglia, using the broad hospital regions. This very roughly corresponds to the appearance of Devonian and other carboniferous rocks in the British Isles.

However, the association between softness of the water and a high incidence of neural tube malformation is very tenuous, for when the water supply and the incidence are examined on a more local level any association disappears—as, for example, in several townships in South Wales which have an incidence of over three times the national average and where the hard water supply is drawn from an artesian well.²

The advantages of having soft water in the home after treatment by a water softener ought not to be discarded on the evidence at present available

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Allergy to Penicillin

Q.—What alternative prophylaxis can be given before dental extraction in a patient with rheumatic endocarditis who is allergic to penicillin?

A.—The object of antibiotic cover for dental extraction in rheumatic subjects is to kill bacteria, particularly streptococci, which enter the blood stream through torn vessels in the socket. The operative word is "kill," since the fact that the antibiotic used must be bactericidal limits the choice. Penicillin is ideal not only in being bactericidal but because most streptococci are highly sensitive to it.

It is usually safe to administer penicillin to a sensitized patient under cover of an antihistamine or prednisone. Among other bactericidal antibiotics streptomycin, kanamycin, and gentamicin are insufficiently active against streptococci, and the choice lies between vancomycin,¹ which is trouble-

some to administer, and cephaloridine, assuming that the patient is not also allergic to this.

Each of these alternatives was proposed not for sensitized patients but for those already under treatment with penicillin, which selects a resistant streptococcal flora in the mouth. R. A. Tozer et al.² found that such streptococci were susceptible to the bactericidal action of cephaloridine and to some extent also to that of erythromycin, and suggest that 0.5 g. cephaloridine should be given before extraction, followed either by a second dose or a short course of erythromycin.

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Eczema in Identical Twins

Q.—One identical twin aged 6 has infantile eczema: the other has a perfect skin. Is this common, and is the unaffected child likely to develop eczematous lesions?

A.—It is very uncommon for only one identical twin to be affected with atopic eczema. While the onset of clinical eczema sometimes varies by a year or two in identical twins, the disease is usually evident in both twins before the age of 6. However, latent atopy can exist, and discordance in identical twins was described by Rajka.¹

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Height and Weight Tables

Q.—In drawing up height/weight tables is a distinction drawn between people with a small, medium, or large frame? If so, how can the size of frame be determined?

A.—Some tables in the past have made a distinction, usually using just circumference as an indication of the size of frame. In my view the distinction is not a very useful one. The real point is why is height used for weight tables at all? Usually tables are used for the control of obesity. If so, then a better guide is measurements of subcutaneous fat by skinfold thickness (measured with a scientifically devised caliper).¹

REFERENCE

- 1 Edwards, D. A. W., Hammond, W. H., Healy, M. J. R., Tanner, J. M., and Whitehouse, R. H., *British Journal of Nutrition*, 1955, 9, 133

Alpha-tocopherol in Cardiovascular Disease

Q.—Is Vitamin E (α -tocopherol) of use in the treatment of intermittent claudication, and, if so, what is its mode of action? Is it of use in treating cardiac ischaemia?

A.—The use of vitamin E (alpha-tocopherol) in cardiovascular disease was first reported in 1947.¹ Clinical improvement was claimed in the anginal syndrome, hypertensive heart disease, and rheumatic heart disease, and later papers by the same authors^{2,3} claimed that vitamin E resolved phlebothrombosis, healed indolent leg ulcers, and produced good or even "excellent" results in intermittent claudication and coronary thrombosis. Such a panacea produces sceptics as well as enthusiasts, and observations of a more controlled nature soon showed that vitamin E was of no value in angina^{4,6} or in hypertensive heart disease.⁶

There has been rather more uncertainty over the value of vitamin E in intermittent claudication. Early observations in Manchester^{7,8} were promising, but the trials were not of the strictly controlled type. A classical double-blind trial with a placebo⁹ showed no benefit attributable to vitamin E, but a similar trial suggested that it might be of some value.¹⁰ The Manchester group reaffirmed their early claims after a "double-blind" trial, but one suspects that the nature of their placebo preparation (lactose) destroyed the double-blind nature of the trial and rendered the exercise tolerance tests subject to bias by the patient.¹¹

The case for vitamin E in intermittent claudication is therefore, at best, not proven. It is an antioxidant, and it has been suggested¹¹ that it may act directly on the energy cycle of the muscle cells rather than on the blood vessels, reducing the requirement for oxygen.

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- 11 Boyd, A. M., and Marks, J., *Angiology*, 1963, 14, 198.